CLINICAL RESEARCH IN GERIATRICS PAST, PRESENT, AND FUTURE*

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THE medical problems inherent in the aging process have a history that is well documented far back in antiquity. An Egyptian hieroglyphic ideograph of 2800 B. C. depicts old age as a bent human figure resting on a staff. In a papyrus of 1580 B. C. this ideograph has the subscript "to be an old man is evil in every respect."[1] This assertion is born out by the prevalence of osteoarthritis, tuberculosis, and parasitic infestation in the mummies of the period.

This ideograph is surprisingly similar to a self portrait of Hokusai at age 80 in the 1800s. He signed his portraits with his age to 87 as did Stradivarius his violins to age 90.

That the changes of aging were well known in biblical times is beautifully expressed in allegorical terms in the Old Testament, attributed to a high priest of about 100 B. C. (Eccles. 12.4 A.V.) He describes loss of vision by comparing old age with "the days of thy youth when the sun, or the light or the moon, or the stars be not darkened", loss of hearing as "when the sound of the grinding is low", senile tremor as "when the keepers of the house shall tremble", weakness as "and the grasshopper shall be a burden", insomnia as "he shall rise up at the voice of a bird" and "desire shall fail" as well as other changes.

Old age was thought to begin much earlier than today as exemplified in Steven Blankaart's *Lexicon Medicum Graeco-Latinum,* published in Amsterdam in 1679. Old age is defined as that part of the course of life from the 50th to the 60th year and what is worse that which follows is "decrepit age which ends in death."[3]

Clinical research in geriatrics has an honorable history dating to biblical times. In Daniel we find "many shall run to and fro, and knowledge shall be increased" (Dan 12.4 A.V.), a perfect description of our annual meetings. In Samuel we find an accident report, a fundamental of research in

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this field, where Eli, the high priest, on receiving the news of the loss of the Ark of the Covenant to the Philistines, "fell from off the seat backward by the side of the gate, and his neck brake, and he died, for he was an old man and heavy" (1 Sam. 4.18 A.V.), demonstrating the effects of emotional strain , obesity, and a seat lacking a back on an old man. Elijah performed an early controlled experiment in his contest with the priest of Baal on the top of Mount Carmel when each presented identical bullocks for sacrifice to their respective deities. Needless to say, Elljah's sacrifice was accepted by incineration and the other was not (1 Kings 18.19-39 A.V.)

In 1863 Canton reported a clinical pathological correlation of arcus senilis using the aged population of the St. Martins in the Fields workhouse of London.[4] He found a correlation with fatty degeneration of the heart as Dr. F. D. Zeman and I found with coronary heart disease in a study during the 1950s.[5]

Research in clinical geropsychiatry may be said to have been begun by Phillipe Pinel who, in the 1700s, advocated and practiced humane treatment of the insane. As head of Bicêtre, the largest institution for the insane in Paris, with the consent of the National Assembly after the revolution, he struck off the chains of 49 insane patients on May 24, 1778.

Charcot, the great French clinician, head of the Salpetriere, a refuge for women, wrote one of the first formal books on aging in 1867. His acute clinical observation is exemplified by such observations with regard to the aged as "the gravest disorders manifest themselves by slightly marked symptoms and they may even pass unnoticed"; "it is in old age that we observe the greatest number of latent disease" and "old women with pneumonia do not even complain of malaise; no one notices the change in their condition. They get up, make their beds, walk about, eat as usual and afterwards, feeling a little tired, they totter to their beds and expire."[6]

Thoms, the curator of the British Museum, in his book entitled *Longevity in Man: Its Facts and Fictions* in 1873, disproved the myth of the supercentenarian, particularly that of Thomas Parr, who claimed 152 years, marrying at 80 and fathering an illegitimate child at 105. With intensive research Thoms could find no proof for these assertions. He notes "I really hardly know which is to be more wondered at, the exceptionally great age attributed to Parr or the fact that for upwards of two centuries nobody has appeared to doubt its accuracy or taken the slightest trouble to ascertain upon what evidence it was founded."[7] He

anticipated our present credulity with regard to ancient Abkasians in the Caucasus and Ecuadorians in the Andes.

Emil Demange made excellent clinical pathological observations on 500 postmortem examinations of residents of the St. Julien Hospice of Nancy, France, in the late 1800s.[8] Seiler, in a monograph published in 1800, admonished physicians connected with homes for the aged to take advantage of their opportunities for adding to knowledge.[9]

With this historical background, what are the principal problems of clinical research in aging today? They may be summarized as to objectives, sources of funding, where it should be carried out, answers to the questions of informed consent and types of research, how physicians and medical students can be motivated to carry on research, what achievements have been accomplished, and the fields demanding major consideration for future effort.

Clinical research in the aged should answer patients' questions: "What is wrong with me and what can you do about it?" Therefore, it is intimately related to clinical practice and social conscience. It is a form of applied science and hence suffers from a dangerous form of scientific snobbism which draws distinctions between pure and applied science. A dedicated clinical scientist must learn to disregard those scientists who say that he is not a proper scientist and those clinicians who say that he is not a proper clinician.

An older generation of clinicians derived satisfaction from contributing something of value and professional status through their unfunded, voluntary efforts in clinical research in aging and made many significant contributions. They pursued their research activities in their own time, often to the dismay of their families. Most had a philosophy that good clinical care was the basis of worthwhile clinical research. The difficulties faced by such researchers in finding the time for reading, obtaining references, preparing tables, graphs, and manuscripts were legion.

From these researchers came a body of knowledge in a wide variety of fields. In cardiology we have had work on silent and atypical myocardial infarction, cardiac arrhythmias, acute and chronic illness in relation to accident liability, the use of digitalis, cardiac rupture, the natural history of conduction disturbances, adjustment to the cardiac pacemaker, and the significance of orthostatic hypotension. The atypical character of pneumonia in the aged was described. Fundamental work was done in senile macular degeneration. In psychiatry we have the earliest work on death and dying, the mental status questionnaire, the face-hand test, brief psychotherapy, the team

conference, the effects of Alzheimer's disease on mortality and functional classification of the aged.[10]

Today, funding is considered essential for the pursuit of clinical research in aging in an economic and political environment where the sources are drying up. Funds must be made available to subsidize not only clinical and basic researchers in geriatrics on full- and part-time bases, but also for medical students during vacation times and to stimulate fellows and resident physicians in the field. By exposure of medical students and house staff to well run institutions for the aged, community centers and housing projects and home health and other community based programs, to care at home and to structured programs in all four years of the medical school program, talented young people will be self selected for future research in clinical geriatrics.

The value of relatively small expenditures in supporting research is evident in the record. Insulin replacement therapy for diabetes cost only $15,000 from the onset of the idea to the delivery of the first insulin for injection into humans. Polio vaccine cost a total of $41 million to develop and test and has saved 70 times that amount in medical costs each year of its use. In 1977 $4,500 was spent for research in chronic brain disorders while six billion dollars were spent for nursing home care for such conditions.

The present trend away from human centered and disease oriented research and the concomitant increase in investigation whose material is neither human nor diseased has been documented by Feinstein and Kass. An analysis of abstracts submitted to the annual meetings of the American Federation for Clinical Research, American Society for Clinical Investigation, and the Association of American Physicians between 1953 and 1967 demonstrated a long-term decrease in the former and increase in the latter. Between 1965 and 1967 only about 2% of the research papers submitted to the subspecialty sections were patient centered.[11] Booth demonstrated a similar trend for the years 1974 to 1979, which he related to the progressive marked decline in the number of clinical scientists both here and in England and their replacement by nonmedical scientists usually holding Ph.D. degrees.[12]

In the aged a reasonable balance of medical research is desirable. Excess emphasis on nonhuman, nondisease studies alienates investigators. Clinical medical research in the aged should result from and lead to good medical care, and should be based on the premise *primum non nocere*.

Informed consent is a difficult problem in research in the aged, particularly among those in long-term-care institutions and in hospitals. Determination of adequate cognitive ability to make such a consent among those with chronic illness, heavily medicated and with varying degrees of fluctuating senile

dementia, both chronic and acute, is difficult.[13] Unfortunately, even though a judgment of incompetence is made on the basis of disorientation, poor judgment, and memory loss, in Alzheimer's disease a degree of reversability with fluctuating impairment of cognition is often complicated by the effects of medication, other psychiatric disorders, and linguistic and other impediments to communication, which make the decision as to whether the consent is really informed difficult.

Attempting to evaluate a degree of cognitive ability sufficient to consent with adequate information and understanding of what is involved by psychological tests in many cases causes more stress than the procedure for which the consent is sought. Calling in a psychiatrist to make the decision communicates a threat to the patient of being labelled mentally imcompetent if he does not comply with the physician's preference.[14] It has been questioned whether institutionalized persons can give truly voluntary consent. They become emotionally dependent on their care givers, and this limits their ability to resist demands upon them. Many would consent to anything suggested. Obtaining consent from guardians has a difficulty in that the law prohibits them from approving research if there is no possible benefit to the subject.[15] New legislation is needed to overcome these difficulties that prevent research into the vast problem of senile dementia. Laws vary from state to state on the subject so that a uniform statute is desirable.[15]

Even among mentally clear individuals aged 20 to 82, a recent study found that on testing for the recall of the significance of the informed consent within one day of signing, only 60% understood the purpose and nature of the procedure, and only 55% correctly listed even one major risk or complication. The more ill the person, the weaker his comprehension.[16]

The question also must be answered whether human research committees inhibit clinical research and to what extent. It is possible that the previously mentioned increase in animal research and decline in human research in part reflects a feeling that it is easier to do animal experiments than to go through the paper work and committee proceedings of human research committees.[13]

The principal types of clinical research studies are cross sectional and longitudinal. Cross-sectional studies are easier and more convenient, but their inherent limitations make them of lesser value. These include secularity, i.e., comparing a group of aged individuals with a younger group, which suffers from the fact that the aged were born around the turn of the century and brought up under markedly different social, economic, nutritional, and cultural conditions, often on another continent.

Cross-sectional studies of a variable related to survival, either because it

has a negative or positive effect, will result in what appears to be an age-related difference which does not exist. For example, in a recent study in progress in which I have been involved, serum total and low density lipoprotein cholesterol content shows a steady downward trend with successively advancing age in a group of 100 women between 67 and 105 years of age. Since both total and low density lipoprotein cholesterol levels have a definite increased effect on mortality from coronary heart disease, we have selective mortality, that is, the more aged members of the group tend to be survivors of a group among whom those with elevated levels of the lipids have died at earlier ages. This will erroneously suggest that the total and low density lipoprotein levels decline with age. In a prospective longitudinal study this effect might well be absent.

Long-term longitudinal studies, following up younger individuals by the use of periodic multiphasic evaluations to old age, are superior because in this way the rate of change of specific functions can be assessed for any given individual. They are not without the disadvantages of costliness, attrition of subjects due to death, lack of interest or relocation, the saddling of the investigator with outmoded methods, and the necessity for recruitment of young staff members who can be expected to outlive the subjects and carry on work begun by older investigators. The introduction of newer diagnostic techniques during the course of such studies will add to their value. Specimens of blood etc. may be frozen for future use as new tests become available.

The establishment of normal laboratory values for the aged is important. We accept without question that infants, children, and adolescents have a changing spectrum of normal values over a period of about 17 years. Yet we tend to accept normal values for adults as valid for the aged over a span of up to 35 years after age 65. We are just beginning to realize how difficult it is to establish normal standards for the aged even in such extensively investigated conditions as hypertension and diabetes mellitus. there is no unanimity of opinion as to the definition of normal glucose tolerance in the aged or as to agreed criteria for treatment. What we used to think were optimal levels of total serum cholesterol have turned out to be related to increased mortality from cancer, especially of the digestive tract. Mild to moderate overweight has been found to be related to improved life expectancy in the aged.[13]

Research establishing normal values by ascending age, as for pulmonary function, is valuable and encouraging in that it shows that if a heavy smoker stops smoking, in 18 to 24 months his pulmonary function returns to normal. While smoking, their levels are those of an individual 10 years older. A pitfall

in determining normal values for the aged is demonstrated by creatinine clearance, whose 24-hour value is used as an index of the glomerular filtration rate and of renal function. In the aged, a parallel decrease occurs in creatinine clearance with aging and of daily creatinine excretion due to decreased muscle mass. The net result is no change in serum creatinine level.[17]

In the mass enthusiasm for the detection and treatment of risk factors for coronary and cerebrovascular disease among the population as a whole, little attention has been paid to their significance in the aged where their prevalence is so great. Of women 65 to 74, 47.6% are hypertensive, 51% hypercholesterolemic, 39% inactive, and 27.2% obese. Among men of the same age, 27.1% are hypertensive, 21.6% hypercholesterolemic, 22.8% cigarette smokers, and 27.1% inactive.[18]

What are the pros and cons of treating such large groups? Clinical research is needed to determine indications for treatment with antihypertensive drugs, particularly since, in the most prevalent form, systolic hypertension, the value of treatment has not as yet been established for the aged. Long-term morbidity and mortality studies of the aged are needed, especially to determine the balance of beneficial effects of treatment versus a host of side effects. Orthostatic hypotension in particular, due to antihypertensive and psychotropic medication, is a major cause of injury and cardiac and cerebrovascular events in the aged. Clinical research in the prevention of such incidents by appropriate dosage or introduction of safer medications is indicated. Many studies have demonstrated that moderate obesity is not a risk factor for coronary heart disease, either for initial or subsequent attacks in the aged.[19]

In the previously noted study of 100 aged women, we could establish no relationship between any serum lipid parameter and coronary heart disease or cerebrovascular disease. This deserves further clinical investigation in a longitudinal study with sophisticated methods for evaluation as to the extent to which subclinical coronary disease in the subgroup without clinical coronary heart disease may account for the lack of difference between this group and the one with clinical coronary heart disease. The effects of activity and exercise in preventing or reducing the incidence of coronary heart disease remains to be established. Despite the known effect of alcohol in elevating levels of the favorable risk factor for coronary heart disease, high density lipoprotein cholesterol, its overall effects on mortality in the aged are not known.

The statement has been made that cigarette smoking is not a risk factor for

coronary heart disease among the aged. This needs study because we know that its overall effect on mortality is unfavorable. The Type A personality, time conscious, driving, perfectionistic, achievement oriented, is said no longer to be a risk factor in the aged.[19] We need to know if this is a loss by selective mortality or a change in personality with aging. Aging women were found to become more aggressive and aging men more passive in the Framingham Study.[20]

The difficulties inherent in epidemiologic research at any age are illustrated in a recent article by the Coronary Drug Project Research Group.

The efficacy of clofibrate in reducing mortality over five years in more than 1,100 men who were treated was compared to more than 2,700 placebo cases. There was no difference in mortality. When good adherers to the therapeutic regimen were compared to poor adherers there was a similar reduction in mortality in the clofibrate and in the placebo group. This may be an expression of the different personality types in adherers and nonadherers over a wide spectrum of life style.[21]

Research by means of long-term prospective randomized studies is needed to establish the effects on morbidity and mortality of these risk factors in the aged. Are the adverse effects of medication and strict diet, exercise, and inhibition of pleasurable activities, i.e., smoking, eating, etc., more than overcome by the beneficial effects of the therapeutic regime?

That a risk factor is positive for coronary heart disease does not mean that treating the risk factor will prevent its adverse effects or not induce others, as is the case with clofibrate with regard to gallstones. The question remains to be solved, particularly among the aged, as to how much intensive coronary care units have contributed to the decrease in mortality from coronary heart disease of the last 15 years. Many epidemiologic authorities indicate that they have made only a small contribution. Other factors, such as diet, exercise, smoking decrease and control of hypertension, are deemed to be of greater importance.[22]

Despite decades of research and hundreds of reports, no definitive statements can be made as to the value of anticoagulants in coronary heart disease in the aged. A recent study in Holland among those over 60 seems to indicate a protective effect versus mortality and recurrent acute myocardial infarction in the aged. There were many exclusions and the age group is not as advanced as many of us deal with. More clinical research is needed, especially because the aged risk cerebral and intestinal bleeding due to an increased sensitivity to anticoagulant drugs.[23]

The etiology of heart failure, present in more than four million Americans,

most of them aged, the end point of so many aging hearts, is not completely understood. In some respects our thinking is not ahead of that of Thomas Hobbes, who in the 17th century regarded the heart as a spring and the failing heart as a worn out spring. Much research remains to be done to discover what happens to the aged myocardial fiber that causes it to fail independent of disease.

The present state of our therapy for heart failure leaves much to be done in the way of clinical research. Our knowledge of digitalis, still the most important form of treatment, had in many respects not, until recently, advanced much beyond that reported by Withering in his account of foxglove in 1785, in which he said "despite opinion, prejudice or error, time will fix the real value upon this discovery."[24] Time has confirmed the value of digitalis in augmenting the contractility of the normal and the failing heart,[25] but has not solved the problem of its narrow toxic therapeutic ratio, which results in an incidence of 7 to 22% of toxicity in hospitalized patients, particularly the aged, receiving digitalis derivatives. The question is still unresolved, and reports are contradictory to the value of digitalis in congestive heart failure in regular sinus rhythm where the condition is clinically controlled with diuretics and low salt diet.[26]

Only in the recent past have we learned how digoxin is excreted by the body. Studies using radioactively labeled digoxin show an initial accumulation of digoxin in the body when small doses are given daily. However, as the amount excreted each day is one third of the total amount accumulated in the body, the amount retained each day inceases until an equilibrium of absorption and excretion is reached about the sixth day, at which time an effective dose is present in the body. Utilization of this method of digitalization in nonemergency situations will reduce the incidence of digitalis toxicity in the aged.[27]

Researchers have also demonstrated the direct relationship between digoxin excretion and renal glomerular filtration rate. Since the latter is only one half of normal in the aged, digoxin is excreted less rapidly by them, indicating the need for a substantial reduction in maintenance dosage.[28] Research has demonstrated that intravenous injection of the same dosage of digoxin will yield twice the blood level in a small aged person as in a large young person. Thus, digitalis sensitivity in the aged may be explained not only by low body potassium and magnesium, but by decreased body size, muscle mass, and renal glomerular filtration.

A problem that needs clinical research in the aged is the indications for supplemental potassium therapy, which are nicely outlined in a paper by

Harrington et al. Do so many aged with hypertension being treated with diuretics need potassium? While we try to determine the indications between the competing risks of fatal arrhythmias in those not given supplements or potassium sparing diuretics, a complication particularly marked in the aged, untold millions of hypertensives are ingesting vast quantities of bananas, orange juice, distasteful potassium salts, potentially dangerous enteric coated tablets, and potassium-sparing diuretics.[29] It has been estimated that in 1981 7.5 million prescriptions for potassium preparations and 19 million for potassium-sparing diuretics at a cost of 250 million dollars were given to patients with "essential benign hypertension."[29]

Vasodilator therapy for the control of heart failure is a recent advance which requires further evaluation in those of advanced age. Questions remain as to whether these drugs which reduce prior and after load of the failed heart can be taken over prolonged periods without development of tolerance in some cases or increased failure on cessation in others. Their effect on life expectancy has not been established.

The value of such newly investigated drugs as verapamil and nifedipine, which block the slow calcium channel of cardiac muscle contraction, in relieving coronary artery spasm with consequent variant angina at rest has to be established in the aged, as has the value of verapamil in paroxysmal atrial tachycardia. Clinical research has shown that the coronary arteries of the aged, which were not supposed to be able to constrict because of atherosclerosis and loss of elasticity, do constrict and produce variant angina.

Clinical research has demonstrated that the combination of digoxin and quinidine leads to a very marked increase in digoxin level and often toxicity. This is similar to the research which revealed that more generic forms of digoxin yielded unpredictable low serum levels. Verapamil also raises serum digoxin levels.

New techniques of continuous monitoring of the heart by electrocardiographic telemetry are valuable aids for research for study of the effects of stress on the heart, such as automobile driving. This technique has shown that episodes of syncope and faintness, with falls and fractures in the aged, otherwise unexplained, are often due to brief periods of brady or tachyarrhythmias. In a series of 59 patients complaining of dizziness, syncope, palpitations, and falls, average age 82, Gordon found 16 with related diagnostic arrhythmias. Twelve of 16 had resting electrocardiograms, which had no findings suspicious for the arrhythmia found on ambulatory monitoring. Medical therapy controlled the arrhythmia in-

eight.[30] However, a temporal correlation must be established between the occurrence of the arrhythmias and the clinical symptoms because arrhythmias are not rare in the asymptomatic aged. In a study which we carried out, many falls in the aged were due to brief episodes of cardiac dysrhythmia, unappreciated by the aged, which, by a final common pathway of decreased cardiac output and pressure with resultant cerebral ischemia, resulted in falls.[31]

Such research is of great value to patients therapeutically and represents a financial benefit since, when positive, it obviates the need for such time-consuming and expensive procedures as computerized axial tomography, electroencephalograms, and elaborate vestibular testing in seeking the origin of their symptoms.

The introduction of intracardiac pacing techniques and electronic pacemakers have prolonged the life span of aged individuals with second- and third-degree heart block to normal. Clinical research is needed to establish the true indications for their use in the sick sinus syndrome where overutilization has been suggested. The introduction of graduated small amounts of electric current in different locations within the heart and at different time intervals in the cardiac cycle have elucidated the significance of the vulnerable and supernormal phases of the cardiac cycle during which an ectopic beat may trigger a fatal arrhythmia, particularly in the course of acute myocardial infarction. Previously inaccessible portions of the conduction system of the heart, such as the Bundle of His and the Bundle of Kent, can now be studied. Surgical therapy of the Wolf-Parkinson-White syndrome is now possible. We shall learn more about the genesis of the potentially preventable ventricular arrhythmias which cause more than half the deaths from coronary artery disease.

Exercise testing has demonstrated that 38% of healthy aged men have an ischemic response to exercise, compared to only 4% of healthy young men.[32] Such research will help in the determination of the benefits of physical conditioning in the aged, which has not yet been settled.

Modern research has found much of interest about the aging heart. Angiocardiography using radioactive technetium during bicycle exercise and at rest demonstrated that at rest age did not affect the left ventricular ejection fraction, end-diastolic volume, or regional wall motion. Age during exercise was related to significant declines in those over 60 in all three factors with progressive increase with aging in the incidence of wall-motion abnormalities. Maximum heart rate and oxygen consumption also decline linearly with age as do maximum stroke volume and cardiac output.[33]

A new and fascinating example of recent complex cardiologic research has just come to fruition after work on dogs. This is the perfection of a method of terminating ventricular fibrillation and flutter, the chief cause of sudden death in this country, probably a million deaths a year. Lead wires are inserted into the heart as with a pacemaker from the implanted electronic mechanism, which senses the onset of the arrhythmia by analysing the electrocardiogram. It then stimulates the heart with 25 joules of current, a small dose compared to the similar stimulation of the heart by external direct current electroconversion of up to 400 joules for atrial and ventricular arrhythmias. The mechanism recycles itself and can give another shock if the first one is unsuccessful.[34]

Summary and Conclusions

What have been the results of our research efforts and improved care of the aged through improvements in finances, housing, nutrition, etc.? It is not generally realized that, in addition to the well-known increase in life expectancy at birth, there has been a recent marked decline in the mortality rate of the extreme aged, those 85 years of age and over.

Rosenwaike et al. have shown a substantial real decline in mortality among those in this age group between 1966 and 1977. Data from Social Security files on Medicare and the National Center for Health Statistics reveal a 20.4% decrease in the age-adjusted mortality rate for cardiovascular disease and a 30.6% decrease in that for cerebrovascular disease. The effect of these reductions in mortality was only mildly reduced by an increase in cancer deaths of 3%.[35]

We may attribute much of this improvement in mortality to the applied effects of clinical research in determining such risk factors as hypertension and cigarette smoking, in developing improved methods of treatment such as intensive care units, in changing diets, activity, etc.

However, more important than increasing life expectancy accompanied by degenerative processes such as Alzheimer's disease, clinical research must be directed to improving the quality of life in old age through treating and ameliorating the changes of aging and disease and in improving man's adjustment to man and the environment. There have been many successes, but more remains to be accomplished.

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